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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/991,628	11/05/1997	JACK L. STOMINGER	HAR-001DV	2823

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TESTA, HURWITZ & THIBEAULT, LLP
HIGH STREET TOWER
125 HIGH STREET
BOSTON, MA 02110

EXAMINER	
DIBRINO, MARIANNE NMN	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 07/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/991,628	Applicant(s) STOMINGER ET AL.	
	Examin r DiBrino Marianne	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/11/03* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-6,11 and 13-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-6,11 and 13-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. In view of the appeal brief filed on 4/11/03, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

2. Claims 3-6, 11 and 13-16 are pending and are presently being acted upon.

The following are new grounds of rejection.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 3-6, 11 and 13-16 are are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the applicant had possession at the time of invention of the claimed inventions.

The instant claims encompass a pharmaceutical preparation for tolerization comprising a pharmaceutically acceptable carrier and an isolated human polypeptide effective for tolerizing an individual to an autoantigen, said human polypeptide consisting essentially of an amino acid sequence corresponding to the core MHC binding residues of a sequence motif for an HLA-DR protein, or consisting essentially of one of SEQ ID NOS: 1-7, or of a polypeptide *having* an amino acid sequence *corresponding* to the core MHC binding residues of a sequence motif for an HLA-DR protein.

The specification does not it provide adequate written description of "human polypeptide *consisting essentially of* an amino acid sequence corresponding to the core MHC binding residues of a sequence motif for an HLA-DR protein", nor consisting essentially of one of SEQ ID NOS: 1-7, nor of a polypeptide *having* an amino acid sequence *corresponding* to the core MHC binding residues of a sequence motif for an HLA-DR protein, nor does it provide adequate written description of what those MHC core binding residues are and wherein the said polypeptide binds to said HLA-DR protein, and wherein the non-MHC binding residues activates autoreactive T cells from a subject having an autoimmune disease and causes tolerization, nor wherein the HLA-DR protein is associated with a human autoimmune disease. The specification does not disclose what amino acid residues are associated with a *human* polypeptide.

The use for the claimed nucleic acids disclosed in the specification is generation of peptides that bind to an HLA-DR protein associated with an autoimmune disease and which activate autoreactive T cells from a subject having an autoimmune disease and cause toloerization.

The transitional phrase "consisting essentially of" defines the scope of a claim with respect to what unrecited additional components, if any, are excluded from the scope of the claim. Absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." See, e.g., PPG, 156 F.3d at 1355, 48 USPQ2d at 1355 ("PPG could have defined the scope of the phrase consisting essentially of' for purposes of its patent by making clear in its specification what it regarded as constituting a material change in the basic and novel characteristics of the invention."). See also In re Janakirama-Rao, 317 F.2d 951, 954, 137 USPQ 893, 895-96 (CCPA 1963). MPEP 2111.03.

The specification does not define the term "human polypeptide *consisting essentially of* an amino acid sequence corresponding to the core MHC binding residues of a sequence motif for an HLA-DR protein". The specification on page 52 at lines 25-27 discloses that the term "core MHC binding residues" means the residues of an epitope corresponding to the P-1 to P-9 positions of a peptide bound to an HLA-DR molecule. The specification further discloses that there are 5 binding pockets in MHC (class II, DR), P1, P4, P6, P7 and P9 (page 19 at lines 17-25), at least two of which (page 19 at lines 29-31, page 20, lines 5-6) are used via consideration of the chemical nature and size of said binding pockets (page 20 at lines 9-23) for determination of the sequence motif of the corresponding peptide that binds to the MHC molecule (page 19 at lines 29-31).

Accordingly, the amino acids at a maximum of three of the motif positions may not be motif amino acids and may actually be deleterious to binding. The PV motif #1 of instant claim 5 has only three defined positions, P1, P4 and P6. O'Sullivan (1991) was relied upon in a previous office action mailed 6/16/99 for the teaching that the presence of putative binding motif residues does not necessarily correlate with actual binding to an MHC molecule because both binders and nonbinders may have the putative motif (last sentence in Abstract). In addition, the amino acid residues outside the "core" may also be deleterious to binding. The art recognizes that in order to be used for generating an immunogenic or tolerogenic response that said peptide must bind MHC and also present an epitope recognized by T cells. The art recognizes that the T cell epitope differs from the amino acids pertinent to MHC binding. There is no written description in the specification of the amino acids that constitute the T cell epitope in the peptide recited in the claim. With the exception of the specific peptides identified by amino acid sequence in the specification, the skilled artisan cannot envision the detailed structure of the encompassed peptides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. In the instant application, the amino acid itself or isolated peptide is required. See Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016.

In addition, the specification discloses that the peptide may be administered in high doses to produce high dose tolerance, as described in WO 94/06828 page 30 at lines 15-18). The cited WO document, however, teaches substituted tolerizing peptides, i.e., peptides that are generated by replacing each amino acid of the immunogenic peptide with a different amino acid residue and testing for tolerized T cells, i.e., ones that will not proliferate when stimulated with low antigen concentrations.

The specification discloses that HLA-DR4 (DRβ1*0401 and DRβ1*0404) and DR β1*0101 are associated with susceptibility to rheumatoid arthritis (paragraph spaning pages 1 and 2), that HLA-DR4 (DRβ1*0402) or a rare HLA-DQ1 (DQβ1*05032) allele (page 2) are associated with the autoimmune disease pemphigus vulgaris. The specification does not disclose the greater than 70 known HLA-DR allotypes, nor their pocket structures or motifs for peptides that bind to them, and association with susceptibility to autoimmune diseases.

In view of the aforementioned problems regarding description of the claimed invention, the specification does not provide an adequate written description of the invention claimed herein. See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1404-7 (Fed. Cir. 1997). In University of California v. Eli Lilly and Co., 39 U.S.P.Q.2d 1225 (Fed. Cir. 1995) the inventors claimed a genus of DNA species encoding insulin in different vertebrates or mammals, but had only described a single species of cDNA which encoded rat insulin. The court held that only the nucleic acids species described in the specification (i.e. nucleic acids encoding rat insulin) met the description requirement and that the inventors were not entitled to a claim encompassing a genus of nucleic acids encoding insulin from other vertebrates, mammals or humans, id. at 1240. The Federal Circuit has held that if an inventor is "unable to envision the detailed constitution of a gene so as to distinguish it from other materials. . .conception has not been achieved until reduction to practice has occurred", Amgen, Inc. v. Chugai Pharmaceutical Co, Ltd., 18 U.S.P.Q.2d 016 (Fed. Cir. 1991). Attention is also directed to the decision of The Regents of the University of California v. Eli Lilly and Company (CAFC, July 1997) wherein is stated: "The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 222 USPQ 369, 372-373 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, as we have previously held, a cDNA is not defined or described by the mere name "cDNA," even if accompanied by the name of the protein that it encodes, but requires a kind of specificity usually achieved by means of the recitation of the sequence of nucleotides that make up the cDNA." See Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606.

5. Claims 3-6, 11 and 13-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 3-6, 11 and 13-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical preparation comprising a human polypeptide consisting of one of SEQ ID NOS: 1-7, does not reasonably provide enablement for the claimed pharmaceutical preparation comprising a human polypeptide *consisting essentially of* an amino acid sequence corresponding to the core MHC binding residues of a sequence motif for an HLA-DR protein, nor consisting essentially of one of SEQ ID NOS: 1-7, nor a polypeptide *having* an amino acid sequence *corresponding* to the core MHC binding residues of a sequence motif for an HLA-DR protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The specification does not disclose how to make/and or use a pharmaceutical preparation comprising a human polypeptide *consisting essentially of* an amino acid sequence corresponding to the core MHC binding residues of a sequence motif for an HLA-DR protein, nor *consisting essentially of* one of SEQ ID NOS: 1-7, nor a polypeptide *having* an amino acid sequence *corresponding* to the core MHC binding residues of a sequence motif for an HLA-DR protein. The specification has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims encompass amino acid residues in the P1-P9 "core" that are non-HLA-DR binding amino acid residues at HLA-DR motif binding positions and additionally encompass proteinaceous material which contains sequences outside of the "core" MHC binding residues of a sequence motif for an HLA-DR protein.

The transitional phrase "consisting essentially of" defines the scope of a claim with respect to what unrecited additional components, if any, are excluded from the scope of the claim. Absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." See, e.g., PPG, 156 F.3d at 1355, 48 USPQ2d at 1355 ("PPG could have defined the scope of the phrase consisting essentially of' for purposes of its patent by making clear in its specification what it regarded as constituting a material change in the basic and novel characteristics of the invention."). See also In re Janakirama-Rao, 317 F.2d 951, 954, 137 USPQ 893, 895-96 (CCPA 1963). MPEP 2111.03.

The specification does not define the term "human polypeptide *consisting essentially of* an amino acid sequence corresponding to the core MHC binding residues of a sequence motif for an HLA-DR protein." The specification on page 52 at lines 25-27 discloses that the term "core MHC binding residues" means the residues of an epitope corresponding to the P-1 to P-9 positions of a peptide bound to an HLA-DR molecule. The specification further discloses that there are 5 binding pockets in MHC (class II, DR), P1, P4, P6, P7 and P9 (page 19 at lines 17-25), at least two of which (page 19 at lines 29-31, page 20, lines 5-6) are used via consideration of the chemical nature and size of said binding pockets (page 20 at lines 9-23) for determination of the sequence motif of the corresponding peptide that binds to the MHC molecule (page 19 at lines 29-31).

Accordingly, the amino acids at a maximum of three of the motif positions may not be motif amino acids and may actually be deleterious to binding. The PV motif #1 of instant claim 5 has only three defined positions, P1, P4 and P6. O'Sullivan (1991) was relied upon in a previous office action mailed 6/16/99 for the teaching that the presence of putative binding motif residues does not necessarily correlate with actual binding to an MHC molecule because both binders and nonbinders may have the putative motif (last sentence in Abstract). In addition, the amino acid residues outside the "core" may also be deleterious to binding. The art recognizes that the T cell epitope differs from the amino acids pertinent to MHC binding. There is no written description in the specification of the amino acids that constitute the T cell epitope in the peptide recited in the claim.

In addition, the specification discloses that the peptide may be administered in high doses to produce high dose tolerance, as described in WO 94/06828 page 30 at lines 15-18). The cited WO document, however, teaches substituted tolerizing peptides, i.e., peptides that are generated by replacing each amino acid of the immunogenic peptide with a different amino acid residue and testing for tolerized T cells, i.e., ones that will not proliferate when stimulated with low antigen concentrations.

The specification discloses that HLA-DR4 (DRβ1*0401 and DRβ1*0404) and DR β1*0101 are associated with susceptibility to rheumatoid arthritis (paragraph spaning pages 1 and 2), that HLA-DR4 (DRβ1*0402) or a rare HLA-DQ1 (DQβ1*05032) allele (page 2) are associated with the autoimmune disease pemphigus vulgaris. The specification does not disclose the greater than 70 known HLA-DR allotypes, nor their pocket structures or motifs for peptides that bind to them, and association with susceptibility to human autoimmune diseases.

Evidentiary reference Chicz et al (J. Exp. Med. 1993, 178: 27-47) teaches that *naturally processed* peptides acid-extracted from a variety of HLA-DR alleles ranged from 10-34 amino acid residues in length (especially Abstract). It was known to the skilled artisan at the time the invention was made that Class II MHC/HLA molecules are capable of binding larger exogenous peptides. The instant claims, do not recite a length limitation for the polypeptide. In addition, particularly in longer polypeptides, the amino acid residues outside of the core amino acid residues would render the polypeptide susceptible to other frames of binding to the HLA molecule than the intended frame consisting of the motif amino acid residues.

There is no guidance in the specification as to what alterations result in a functional polypeptide, i.e., one that binds to HLA-DR (except for 3 defined of 5 HLA-DR4 binding positions) and to a TCR and causes tolerization. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions/additions would be acceptable to retain functional activity, i.e., bind to any number of undisclosed HLA-DR molecules, bind to a T cell and cause tolerization, it would require undue experimentation for one of skill in the art to arrive at amino acid sequences that would have functional activity. In other words, since it would require undue experimentation to identify amino acid sequences that have functional activity, it would require undue experimentation to make and/or use the corresponding sequences. The enablement provided by the specification is not commensurate with the scope of the claims.

The following rejections remain.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 13-16 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 13 is indefinite in the recitation of "wherein said preparation is *free* of a polypeptide corresponding to said sequence" because it is not clear what is meant. The instant claim 13 recites a pharmaceutical preparation comprising an amount of an immunogenic preparation effective to immunize against a human pathogen that in its native form *includes* a polypeptide that has a sequence that binds to an HLA-DR protein.

b. Claim 13 is indefinite in the recitation of "includes a polypeptide" because it is not clear whether said polypeptide is a portion of a protein from a pathogenic organism.

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 3-6 and 13-16 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 3 of U.S. Patent No. 5,874,531. Although the conflicting claims are not identical, they are not patentably distinct from each other because the composition comprising the peptides of claim 3 of the '531 patent are encompassed by the instant claims.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 3-5 and 13-15 stand rejected under 35 U.S.C. 102(b) as being anticipated by Amagai et al (Cell, Vol. 67, pages 869-877, 1991) for the reasons of record in Paper No. 12 mailed 6/16/99.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 703-308-0061. The examiner can normally be reached on Monday and Thursday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Chan, can be reached on (703) 308-3973. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.
Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Marianne DiBrino, Ph.D.
Patent Examiner
Group 1640
Technology Center 1600
July 11, 2003

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600